Remarks

Claims 21-45 were pending in the subject application. By this Amendment, claims 21, 24, 26, 29, 31, 37, and 39 have been amended, claims 22-23, 27-28, 38, 44, and 45 have been cancelled, and new claims 46-58 have been added. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of the applicant's agreement with or acquiescence in the Examiner's position. Accordingly, claims 21, 24-26, 29-37, 39-43, and 46-58 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

Submitted herewith is a Request for Continued Examination (RCE) under 37 C.F.R. §1.114, including a request for a suspension of action under 37 C.F.R. §1.103(c). A supplemental Information Disclosure Statement (IDS) is submitted herewith for the Examiner's consideration. The applicant requests that the references listed on the accompanying Form PTO/SB/08 be made of record in the subject application and that the Examiner's consideration of these references be made of record.

The applicant and the applicant's representative wish to thank Examiner Qian for the courtesy of the telephonic interview conducted with the undersigned on December 19, 2005, regarding the rejection of claims 22 and 31-45 under 35 U.S.C. §112, first paragraph, and the rejection of claims 21 and 23-30 under 35 U.S.C. §102(b). The remarks and amendments set forth herein are consistent with the substance of the interview and are believed to address the outstanding issues as discussed during the interview.

By this Amendment, claims 46-58 have been added. Support for claim 46 can be found, for example, at page 2, lines 4-21, page 3, lines 10-19, page 5, lines 9-18, and page 6, lines 3-15. Support for claim 47 can be found, for example, at page 2, lines 10-12. Support for claim 48 can be found, for example, at page 3, lines 25-31, and page 4, lines 1-16 and 20-21. Support for claims 49 and 56 can be found, for example, at page 2, lines 25-28. Support for claims 50-52 and 54 can be found, for example, at page 2, lines 4-6, and page 4, lines 22-24. Support for claim 53 can be found,

for example, at page 2, lines 22-24, and page 4, lines 28-30. Support for claim 55 can be found, for example, at page 3, lines 25-31, and page 4, lines 1-16 and 20-21. Support for claims 57 and 58 can be found, for example, at page 7, lines 1-4.

Claims 22 and 31-45 have been rejected under 35 U.S.C. §112, first paragraph, as non-enabled by the subject specification. The applicant respectfully traverses and submits that the claims are fully enabled by the subject specification.

The cells, compositions, and methods of the claimed invention are reasonably enabled by the specification, as one of ordinary skill in the art would be able to make and use the invention without undue experimentation.

By this Amendment, claims 21 and 26 have been amended to recite that the conditionally immortal hematopoietic stem cells (HSC) are human cells. Thus, claims 21-29 are drawn to conditionally immortal human hematopoietic stem cells and compositions containing such cells. As discussed during the telephonic interview, "when a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for non-enablement based on how to use" (emphasis added) MPEP 2164.01(c). In addition to the treatment of neurological disorders taught in the specification, conditionally immortal hematopoietic stem cells (HSC) are useful *in vitro* or *in vivo* for many of the same purposes as other HSC. For example, as taught at page 3, lines 30-31, and page 4, lines 1-3 of the specification, the conditionally immortal HSC can be expanded *ex vivo* under permissive culture conditions and exposed to non-permissive conditions for differentiation. The differentiated cells can then be used as a source of various blood cell types. Similarly, conditionally immortal HSC can be expanded in culture and the differentiated cells can be used as a source of hematopoietic proteins. The conditionally immortal HSC can be genetically modified and used as a source of heterologous gene products (see WO 92/11355; WO 93/18137, and U.S. Patent No. 5,958,767, which are cited at page 1, lines 18-23, and page 7, line 4, of the specification, and of record). Claims 57 and 58 recite that the cells have been genetically transformed to express a heterologous therapeutic gene product. Furthermore, HSC transplants are also routinely used to treat patients with cancers and disorders of the blood and immune system (such as leukemia).

At page 4, the Office Action indicates that the specification only discloses making conditionally immortal HSC by transducing the HSC with an oncogene. By this Amendment, the applicant has amended claims 21, 26, and 37 to recite that conditional immortality is conferred to the cells by an oncogene. Support for these amendments can be found, for example, at page 3, lines 25-31, and page 4, lines 1-21, of the subject specification. The applicant respectfully submits that there is no objective reason for limiting the mode by which the oncogene is introduced into the HSC to transduction. As long as the specification discloses at least one method for making the claimed invention that bears a reasonable correlation to the entire scope of the claim, then "method of making" portion of the enablement requirement of 35 U.S.C. §112, first paragraph, is satisfied (*In re Fisher*, 166 USPQ 18, 24 (CCPA 1970); MPEP 2164.01(b). Other modes of gene delivery were available to those skilled in the art at the time the application was filed. The Office Action does not provide any scientific reasoning to doubt that other modes of gene delivery may be utilized.

At page 5, the Office Action cites page 45 of the NIH report "Stem Cells: Scientific Progress and Future Research Directions" and indicates that *in vitro* long-term bone marrow culture systems have a limited life span. The Office Action appears to be suggesting that the numbers of HSC are too limited. The full-text of the NIH report is submitted herewith for the Examiner's consideration. While it is true that the ability to quickly expand numbers of human HSC would facilitate all current and future medical uses of HSC, pages 51-52 of the NIH report make it clear that human HSC have been used clinically for several years. Furthermore, the NIH report states that almost one-third of cell-based gene therapy clinical trials in the United States have used human hematopoietic stem cells.

> To date, about 40 percent of the more than 450 gene therapy clinical trials conducted in the United States have been cell-based. Of these, approximately 30 percent have used human stem cells—specifically, blood-forming, or hematopoietic, stem cells, as the means for delivering transgenes into patients (page 100, second column, of the NIH report).

At page 5, the Office Action indicates that "although oncogenes such as SV40 large T antigen is well known in the art for immortalizing primary cells into clonal cell lines, whether such application can yield immortalized HSC is unpredictable due to the problems such as our lack of sufficient knowledge of growth conditions of HSC and limited number of true HSC...". The

enablement requirement does not necessarily require that the starting materials for an invention be abundant, only available in sufficient quantities to carry out the invention. Clearly, the state of the art in human HSC culture has not prevented use of these cells in a large number of cell-based gene therapy trials.

The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. A specification disclosure that contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. §112, first paragraph, unless there is reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support. The Office Action cites no reasons to doubt why methods used to conditionally immortalize other cells in the prior art could not be applied to HSC, including human HSC, using the guidance provided in the subject specification.

A copy of WO 97/10329 was submitted with the applicant's previous response. Three currently pending U.S. applications that claim priority to WO 97/10329 include serial no. 09/760,274, filed January 12, 2001, serial no. 10/376,119, filed February 28, 2003, and serial no. 11/178,216, filed July 8, 2005. A Notice of Allowance has recently been mailed to the applicant in serial no. 09/760,274. WO 97/10329 and the foregoing U.S. applications are relevant because they teach transduction of pluripotent neuroepithelial cells with an oncogene to render the cells conditionally immortal (see, for example, page 5, lines 32-36, page 6, and page 12, lines 10-23 of WO 97/10329). Again, the Office Action in the subject application cites no reasons to doubt why methods used to conditionally immortalize other cells in the prior art could not be applied to HSC, including human HSC, as taught in the subject specification. Furthermore, the Office Action provides no scientific reasoning to doubt that the intracerebrally administered HSC function consistently with a neural phenotype, as evidenced by the detected neural markers.

Accordingly, the applicant respectfully submits that, given the teaching of the specification, one of ordinary skill in the art could make and use the claimed invention without the need for undue experimentation. In view of the foregoing remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 21 and 23-30 have been rejected under 35 U.S.C. §102(b) as being anticipated by Nakatsuji *et al.* (*Cell Structure and Function*, 1996, 21(6):624). The applicant respectfully submits that the cited reference does not teach the cells and compositions of the subject invention. However, by this Amendment, the applicant has amended claims 21 to recite that the conditionally immortal hematopoietic stem cells are human cells, as recited in dependent claim 22, which was not included in rejection under §102(b). Claim 22 has been canceled to avoid redundancy. Dependent claim 27 also recites that the conditionally immortal hematopoietic stem cells are human cells. Therefore, during the telephonic Examiner interview, Examiner Qian indicated that claim 27 was mistakenly included in the rejection under §102(b). By this Amendment, the applicant has amended claim 26 to recite that the conditionally immortal hematopoietic stem cells are human cells. Claim 27 has been canceled to avoid redundancy. The Nakatsuji *et al.* abstract describes cell lines established from mouse embryos harboring the SV40 tsA58 gene. Mouse cells obtained from the yolk sac region differentiated into cells having the appearance of macrophages and megakaryocytes. Mouse cells obtained from the ventral trunk region were not evaluated for differentiation potency at the time of publication. The Nakatsuji *et al.* abstract does not teach or suggest an isolated conditionally immortal human hematopoietic stem cell.

Accordingly, claims 21 and 26 have been amended to recite the respective limitations of claims 22 and 27, which the Examiner has excluded from the rejection under §102(b). In view of the foregoing remarks and amendments to the claims, reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b), is respectfully requested.

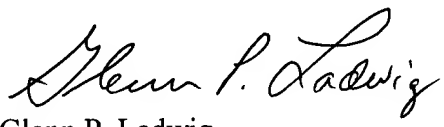
Claim 45 has been objected to as being dependent upon a cancelled base claim. By this Amendment, claim 45 has been amended to depend from claim 31. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

In view of the foregoing remarks and amendments to the claims, the applicant believes that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicant invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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Attachments: Petition and Fee for Extension of Time
Amendment Transmittal Letter
Request for Continued Examination (RCE) under 37 C.F.R. §1.114
Supplement Information Disclosure Statement with form PTO/SB/08 and references